AF/1615
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Re: Appeal to the Board of Patent Appeals and Interferences

In re PATENT Application of Muller

Group Art Unit: 1615

Application No. 09/915,549

Examiner: Humera N. Sheikh

For: DISPERSIONS FOR THE FORMULATION OF SLIGHTLY OR POORLY SOLUBLE AGENTS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Filed: July 27, 2001

Date: June 8, 2004

Sir:

1 ☐ **NOTICE OF APPEAL**: Applicant hereby appeals to the Board of Patent Appeals and Interferences from the decision (not Advisory Action) dated 9/12/2003 of the Examiner twice/finally rejecting claims 1-15, 19-66, 143, 144, 146, and 148-150

2 ☒ **BRIEF** on appeal in this application attached in triplicate.

3 ☐ An **ORAL HEARING** is respectfully requested under Rule 194 (due two months after Examiner's Answer – unextendable).

4 ☐ Reply Brief is attached in triplicate (due two months after Examiner's Answer – unextendable).

5 ☒ "Small entity" verified statement filed: ☐ herewith. ☒ previously.

6 **FEE CALCULATION:**		Large/Small Entity	
If box 1 above is X'd, see box 12 below first and decide: ..... enter		$	$ 165
If box 2 above is X'd, see box 12 below first and decide: ..... enter		$	$
If box 3 above is X'd, see box 12 below first and decide: ..... enter		$	$
If box 4 above is X'd, ... enter nothing		- 0 - (no fee)	
7. Original due date: May 10, 2004			
8. **Petition is hereby made** to extend the original due date to cover the date this response is filed for which the requisite fee is attached	(1 months) (2 months) (3 months) (4 months) (5 months) $$$$$	55	
9. Enter any previous extension fee paid [ ] previously since above original due date (item 7); [ ] with concurrently filed amendment			
10. **Subtract line 9 from line 8 and enter: Total Extension Fee**			+55
11. **TOTAL FEE ATTACHED =**			**$215**

12. ☐ *Fee NOT required if/since paid in prior appeal in which the Board of Patent Appeals and Interferences did not render a decision on the merits.

CHARGE STATEMENT: The Commissioner is hereby authorized to charge any fee specifically authorized hereafter, or any missing or insufficient fee(s) filed, or asserted to be filed, or which should have been filed herewith or concerning any paper filed hereafter, and which may be required under Rules 16-18 (missing or insufficient fee only) now or hereafter relative to this application and the resulting Official document under Rule 20, or credit any overpayment, to our Account/Order Nos. 50-0687/62662 for which purpose a duplicate copy of this sheet is attached. **This CHARGE STATEMENT does not authorize charge of the issue fee until/unless an issue fee transmittal form is filed.**

Manelli Denison & Selter, PLLC

Att:: Jeffrey S. Melcher

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT Application of Muller

Group Art Unit: 1615

Application No. 09/915,549

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For: DISPERSIONS FOR THE FORMULATION OF SLIGHTLY OR POORLY SOLUBLE AGENTS

* * * * *

June 8, 2004

APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal from the final rejection of claims 1-15, 19-66, 143, 144, 146 and 148-150 of the subject application.

This Appeal Brief is submitted in triplicate as required by 37 C.F.R. § 1.192 (a).

1. Real Party in Interest:

This application is assigned to PharmaSol GmbH.

2. Related Appeals and Interferences:

There are no other appeals or interferences known to Appellant, the Appellant's legal representative, or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

3. Status of Claims:

Claims 1-150 are pending in this application. Claims 16-18, 67-142, 145 and 147 stand withdrawn from consideration pursuant to a Restriction Requirement.

The rejection of claims 1-15, 19-66, 143, 144, 146 and 148-150 is appealed. Please see the Appendix for a copy of the claims under appeal.

4. Status of any Amendment Filed Subsequent to Final Rejection:

No amendments have been filed subsequent to final rejection.

A Notice of Appeal was filed on March 10, 2004, along with the appropriate extension petition and fee.

5. Concise Explanation of the Invention:

Claim 1 recites a dispersion comprising an oily phase, an aqueous phase, in the form of an oil-in-water emulsion or a water-in-oil emulsion, and at least one active ingredient that is only slightly or with difficulty soluble in the oily phase and the aqueous phase. The dispersion is free from toxicologically dangerous organic solvents and contains the active ingredient dissolved in a quantity that is greater than the quantity which results additively from its maximum solubility in the oily and the aqueous phase of the emulsion. Basis for this claim can be found on page 5, lines 1-10, page 6, line 33 to page 7, line 2, and page 14, line 33 to page 15, line 2.

Claim 2 recites that the active ingredient, in addition to the dissolved state, is partially present in highly dispersed solid crystalline form, resulting in a dispersion with a

heterogeneously dispersed phase of oil drops and active ingredient crystals. Basis for this claim can be found on page 5, lines 25-28. Claim 3-11 are dependent upon claim 2 and recite specific amounts and sizes of active ingredients as follows, at that at least 90% of the active ingredient crystals present are smaller than 5 μm (claim 3); at least 95% of the active ingredient crystals present are smaller than 5 μm (claim 4); wherein about 100% of the active ingredient crystals present are smaller than 5 μm (claim 5); wherein at least 90% of the active ingredient crystals present are smaller than 3 μm (claim 6); wherein at least 95% of the active ingredient crystals present are smaller than 3 μm (claim 7); wherein about 100% of the active ingredient crystals present are smaller than 3 μm (claim 8); wherein at least 90% of the active ingredient crystals present are smaller than 1 μm (claim 9); wherein at least 95% of the active ingredient crystals present are smaller than 1 μm (claim 10); and wherein about 99% of the active ingredient crystals present are smaller than 1 μm (claim 11), volume distribution determined by laser diffractometry. Basis for these claims can be found at page 8, lines 16-24 and page 13, line 24 through page 14, line 2.

Claims 12-15 recite specific amounts of aqueous phase in claim 1, wherein the dispersion comprises an oil-in-water emulsion and contains about 5 to about 99.5 wt.% of aqueous phase (claim 12); wherein the dispersion comprises an oil-in-water emulsion and contains about 10 to about 95 wt.% of aqueous phase (claim 13); wherein the dispersion comprises an oil-in-water emulsion and contains about 60 to about 95 wt.% of aqueous phase (claim 14); and, wherein the dispersion comprises an oil-in-water emulsion and contains about 70 to about 95 wt.% of aqueous phase (claim 15), based

on the total weight of the dispersion. Basis for these claims can be found at page 11, lines 6-9.

Claim 19 recites that the dispersion of claim 1 contains at least one selected from the group consisting of emulsifiers and stabilizers. Claims 16-23 recite different amounts for the emulsifiers and stabilizers of claim 19, wherein the dispersion contains less than 15 wt.% of emulsifiers and/or stabilizers (claim 20); wherein the dispersion contains less than 10 wt.% of emulsifiers and/or stabilizers (claim 21); wherein the dispersion contains less than 2 wt.% of emulsifiers and/or stabilizers (claim 22); and wherein the dispersion contains from about 0.6 to about 1.2 wt.% of emulsifiers and/or stabilizers (claim 23), based on the total weight of the dispersion. Basis for these claims can be found at page 12, line 29, and page 14, lines 19-31.

Claim 24 recites preferred emulsifiers, wherein the dispersion comprises at least one emulsifier selected from the group consisting of egg lecithin, soya lecithin, phospholipids of egg or soya, sorbitan esters, sorbitane trioleate, polyethylene glycol sorbitan esters, polyoxyethylene sorbitane monooleate, sodium glycocholate, sodium lauryl sulphate, and mixtures thereof. Basis for this claim can be found at page 9, lines 11-24.

Claim 25 recites that the dispersion of claim 1 comprises at least one stabilizer selected from the group consisting of block co-polymers, poloxamers, Poloxamer 188 and 407, poloxamines, Poloxamine 908, polyvinyl pyrrolidone, polyvinyl alcohol, gelatine, polysaccharide, hyaluronic acid, chitosan, derivatives of chitosan, polyacryl acid, derivatives of polyacryl acid, polycarbophil, cellulose derivatives, methyl cellulose,

hydroxypropyl cellulose, carboxymethyl cellulose, sugar esters, saccharose monostearate, sodium citrate individually, and mixtures thereof. Basis can be found at page 9, lines 11-24.

Claim 26 recites that the dispersion comprises an oil-in- water emulsion and the oil phase used for the preparation of the dispersion comprises lipids which are solid at room temperature. Basis can be found at page 11, lines 20-24.

Claim 27 recites that the dispersion comprises an oil-in- water emulsion and the oil phase used for the preparation of the dispersion comprises lipids which are liquid at room temperature. Basis can be found at page 12, line 5.

Claim 28 recites that the dispersion comprises an oil-in- water emulsion and the oil phase used for the preparation of the dispersion comprises a mixture of one or more lipids which are liquid at room temperature with one or more lipids which are solid at room temperature. Basis for this claim can be found at page 12, lines 5-14. Claim 29 recites that the mixture of liquid lipid:solid lipid varies from about 99:1 to about 1:99 parts by weight, claim 30 recites that the proportion of liquid lipid in mixture of lipids is at least 10 parts by weight, claim 31 recites that the proportion of liquid lipid in mixture of lipids is at least 30 parts by weight, and claim 32 recites that the proportion of liquid lipid in mixture of lipids is at least 50 parts by weight. Basis for these claims can be found at page 11, lines 20-24.

Claim 33 recites that the oil phase comprises at least one individual lipid or mixtures thereof selected from the group consisting of natural and synthetic triglycerides, natural and synthetic monoglycerides, natural and synthetic diglycerides,

self-emulsifying modified lipids, natural and synthetic waxes, fatty alcohols, esters of fatty alcohols, ethers of fatty alcohols, hard wax, Imwitor 900, glycerol trilaurate, glycerol myristate, glycerol palmitate glycerol stearate, glycerol behenat, waxes, cetyl palmitate, carnauba wax, white wax, hydrocarbons, and hard paraffin. Basis can be found at page 12, lines 5-14.

Claim 34 recites that the oil phase comprises at least one selected from the group consisting of soya oil, safflower oil, long-chain triglycerides, medium-chain triglycerides, miglyols, fish oils, oils with an increased constituent of unsaturated fatty acids, and acetylated partial glycerides. Basis can be found at page 9, lines 1-5.

Claim 35 recites that the aqueous phase comprises water or mixtures of water with water-miscible organic liquids and Claim 36 recites that the aqueous phase comprises water and at least one liquid polyethylene glycol. Basis can be found at page 9, lines 25-28.

Claim 37 recites that the aqueous phase contains at least one additive selected from the group consisting of electrolytes, non-electrolytes, glycerol, glucose, mannitol, xylite, gel forming agents, cellulose, and cellulose derivatives. Basis can be found at page 9, lines 30-33.

Claim 38 recites that the liquid and oily phase comprises at least one oil-in-water emulsion selected from the group consisting of Lipofundin, Intralipid, Lipovenoes, Abbolipid, Deltalipid and Salvilipid. Basis can be found at page 8, lines 33-36.

Claim 39 recites that the active ingredient is selected from the group consisting of medical drugs for treatment of human or animal bodies, and claim 40 recites that the

dispersion contains one or more active ingredients selected from the group consisting of anaesthetics, antibiotics, antimycotics, antiinfectives, corticoids, hormones, antiestrogens antiseptics, vasoactivating agents, glauco agents, beta blocker, cholinergics, sympathomimetics, carboanhydrase inhibitors, mydriatics, virustatics, agents for tumor therapy, antiallergics, vitamins, antiinflammytory drugs, immuno-supressives, ciclosporine, and any combination thereof. Basis can be found at page 10, lines 1-5 and lines 20-25, page 14, lines 13-17, page 15, line 8 through page 16, line 14, and examples.

Claim 41 recites that the dispersion is positively charged, claim 42 recites that the dispersion comprises at least one positively charged stabilizer, claim 43 recites that the dispersion comprises at least on positively charged stabilizer selected from the group consisting of sodium lauryl sulfate, stearylamine, positively charged phospholipids, and positively charged lipids, claim 44 recites that the dispersion comprises an oil-in-water emulsion adapted for intravenous injection, and wherein the dispersion comprises at least on positively charged stabilizer, claim 45 recites that the e dispersion further includes at least one lecithines or nonionic stabilizers, and claim 46 recites that the dispersion further comprises at least one poloxamer polymer. Basis can be found at page 16, lines 31-37.

Claim 47 recites that the active ingredient comprises ciclosporine, and claim 48 recites that the active ingredient comprises at least one selected from the group consisting of anti-mycotics, Amphotericin B, anti-infectives, Buparvaquone, Atovaquone, immuno-suppressives, Cyclosporin A, natural and synthetic derivatives of

Cyclosporin A, tumor therapy drugs, Paclitaxel, and Taxotere. Basis can be found at page 15, lines 8-19.

Claim 49 recites that the active ingredient has a solubility of less than 1 part per 100 parts in the aqueous phase, claim 50 recites that the active ingredient has a solubility of less than 1 part per 1000 parts in the aqueous phase, claim 51 recites that the active ingredient has a solubility of less than 1 part per 10,000 parts in the aqueous phase, claim 52 recites that the active ingredient has a solubility of less than 1 part per 100 parts in the oily phase, claim 53 recites that the active ingredient has a solubility of less than 1 part per 1000 parts in the oily phase, and claim 54 recites that the active ingredient has a solubility of less than 1 part per 10,000 parts in the oily phase. Basis for these claims can be found at page 7, lines 4-7.

Claim 55 recites that the size of water phase and oily phase droplets is less than about 10 μm, claim 56 recites that the size of water phase and oily phase droplets is less than about 5 μm, and claim 57 recites that the size of water phase and oily phase droplets is less than about 1 μm. Basis for these claims can be found at page 12, lines 15-22.

Claim 58 recites that the pH of the dispersion is between 4 and 8, claim 59 recites that the pH of the dispersion is between 5 and 7.5, and claim 60 recites that the pH of the dispersion is between 6 and 7.5. Basis for these claims can be found at page 14, lines 9-11.

Claim 61 recites that the active ingredient is present in an amount of from about 0.01 to about 30 wt.%, based on the total weight of the dispersion, claim 62 recites that

the active ingredient is present in an amount of from about 0.1 to about 10 wt.%, based on the total weight of the dispersion, and claim 63 recites that the active ingredient is present in an amount of from about 1 to about 5 wt.%, based on the total weight of the dispersion. Basis for these claims can be found at page 15, lines 4-6.

Claim 64 recites that the quantity of active ingredient dissolved is greater than the additive quantity by a factor of 2, claim 65 recites that the quantity of active ingredient dissolved is greater than the additive quantity by a factor of 5, and claim 66 recites that the quantity of active ingredient dissolved is greater than the additive quantity by a factor of 10. Basis for these claims can be found at page 3, lines 16-24.

Claim 143 recites a medicament comprising the dispersion according to claim 1, claim 144 recites a medicament for treatment of mycoses, inflammations, allergic diseases, tumor diseases, cardiovascular diseases, viral and other infections, or for conducting anaesthetic treatment comprising a dispersion according to claim 1, claim 145 recites a medicament which can be administered intravenously, intra- and subcutaneously, intramuscularly, intra-articularly or intraperitoneally comprising a dispersion according to claim 1, and claim 146 recites a medicament which has a prolonged residence time in the blood, compared to negatively charged dispersions, comprising a dispersion according to claim 1. Basis for these claims can be found at page 10, lines 5-36 and page 15, line 8 through page 17, line 6.

Claim 149 recites dispersions in form of an oil-in-water emulsion comprising an oil phase, a water phase, one or more surfactants or stabilizers, and one or more drugs being only slightly or poorly soluble in the water and in the oil, the dispersions are

supersaturated and contain an incorporated amount of the drug in dispersion that is higher than the additive solubility calculated from the drug solubility in the oil and water phases of the dispersion, and the dispersions are organic solvent-free. Basis for this claim can be found on page 5, lines 1-10, page 6, line 33 to page 7, line 2, and page 14, line 33 to page 15, line 2.

Claim 150 recites that the concentration of surfactant, stabilizer or mixtures of surfactants and stabilizers is between 0.1% and 20% by weight. Basis can be found at page 9, lines 21-23.

These supersaturated dispersions can be formed by adding an active ingredient to the aqueous phase or the oil phase in particle form and then subjecting all components to a fairly high- or high-energy process such as, for example, homogenization, especially high pressure homogenization. The high-energy process of high pressure homogenization leads to incorporation of the active ingredient into the emulsion by molecular dispersion, and no active ingredient crystals remain detectable in the polarization microscope. However, if desired, small injectible active ingredient crystals may remain in the dispersion along with dissolved active ingredient. The emulsions obtained surprisingly have a stability similar to that of systems produced using organic solvents. See page 5, lines 1-10 of the present specification.

6. Issues

I. Whether claims 1-15, 19-25, 33-35, 37-46, 48, 55-57, 61-63, 143, 144, 146 and 148 are patentable under 35 U.S.C. § 102(b) over EPO 0 296 845 (Davis).

II. Whether claims 1-11, 19-25, 33-35, 37-45, 48, 55-57, 61-63, 143, 144, 146 and 148 are patentable under 35 U.S.C. § 102(b) over U.S. patent No. 5,616,330 (Kaufman).

III. Whether claims 1-15, 19-66, 143, 144, 146 and 148-150 under 35 U.S.C. § 103 as being unpatentable over Davis alone or Kaufman alone.

7. Grouping of Claims:

With regard to the anticipation rejection based on Davis, claims 1, 12-15, 19-25, 33-35, 37-46, 48, 55-57, 61-63, 143, 144, 146 and 148 stand or fall together.

With regard to the anticipation rejection based on Kaufman, claims 1, 19-25, 33-35, 37-45, 48, 55-57, 61-63, 143, 144, 146 and 148 stand or fall together.

With regard to the obviousness rejection based on Davis or Kaufman, claims 1, 12-15, 19-63, 143, 144, 146 and 148 stand or fall together and claims 149 and 150 stand or fall together.

Each of claims 2-11 and claims 64-66 do not stand or fall with any other claim.

8. Arguments

From the Examiner's comments regarding the prior art rejections, it is clear that the claimed creation of **supersaturated** emulsions (i.e. producing emulsions which contain a drug concentration being well above the maximum soluble combined amount of the water and the oil phase) and the exclusion of organic solvents was once again improperly dismissed.

The terms "saturation solubility" and "supersaturated systems" are well-known by those of ordinary skill in the art as follows:

The saturation solubility is the **maximum** concentration of a compound in a liquid at a certain temperature and excess compound will be present in form of a non-dissolved precipitate. In case a system consists not only of one liquid but two (e.g. emulsion consisting of water and oil), the total saturation solubility (saturation concentration) of the system (emulsion) is the addition of the saturation solubilities in each of the liquids.

In a supersaturated system, the drug concentration dissolved **is above the saturation solubility**. Such systems can be formed for example when a saturated solution is cooled. The drug does not yet precipitate despite that its concentration is above the saturation solubility, because of the lack of crystallization cores. Such supersaturated systems have pharmaceutical benefits but are in general metastable and very difficult to achieve, which means they exist for a short time, often only minutes before the drug crystallizes out of solution.

When simply dissolving a drug, e.g., in an oil as done by the cited references, only systems at the saturation solubility can be obtained. Routine experimentation by simply trying to dissolve different concentrations in the oil will not lead to a stable supersaturated system.

The present invention relates to novel supersaturated systems that are prepared by novel preparation processes. The drug concentrations in the systems of the present invention are well above the saturation solubility obtained by prior art methods.

A typical example of a poorly soluble drug is Amphotericin B. The limitation in solubility leads to undesirably large injection volumes, or in many cases reaches volumes too large to be administered to a patient. An example is the maximum solubility of Amphotericin B (1mg/mL) in the o/w emulsion, such as in the presently cited Davis. The present invention allows the incorporation of drugs in concentrations above the saturation solubility of the drug in the emulsion (total solubility = amount of drug in

water plus amount of drug in oil). The present invention allows one to reach supersaturation in the emulsions, i.e. going beyond the previously known maximum solubilities. For example, instead of 1 mg/ml (maximum solubility in oil/water), the incorporated amount can now be doubled to a concentration of 2mg/ml (supersaturation). In variants of the invention, concentrations of 5-10mg/mL can even be achieved, i.e. 5 to 10 times greater concentration than the prior art. None of the cited references anticipates, teaches or suggests such stable supersaturation in a formulation.

Oil and water emulsions have been used since the seventies to deliver drugs intravenously. The drugs are typically dissolved in the oil of the emulsion. The cited references teach to use organic solvents to facilitate dissolution of poorly soluble drugs in the oils, which is common practice. Alternatively drugs can be incorporated via a lecithin blend using organic solvents. Low solubility is a major problem and usually results in a drug that cannot be administered intravenously due to the large amount of carrier required. This problem is solved by the present invention by providing a stable supersaturated formulation without using toxic organic solvents.

I. **Claims 1-15, 19-25, 33-35, 37-46, 48, 55-57, 61-63, 143, 144, 146 and 148 are patentable under 35 U.S.C. § 102(b) over EPO 0 296 845 (Davis).**

In the final Office Action, the Examiner rejected claims 1-15, 19-25, 33-35, 37-46, 48, 55-57, 61-63, 143, 144, 146 and 148 under 35 U.S.C. § 102(b) over EPO 0 296 845 (Davis). The Appellant respectfully submits that the Examiner has not provided a prima facie case of anticipation and even if a prima facie case has been provided, the claimed invention is not anticipated by Davis for the following reasons.

The first difference between the present invention and Davis is that Davis needs to use organic solvents to produce the emulsion. Consequently even after removal of the solvent by classical, well-known means a residue of solvent will remain in the

emulsion, which can cause toxicological problems and even may prevent registration with the authorities in case the contamination level is too high. In addition, removal of the organic solvent is a costly process. The claimed invention is organic solvent-free because no organic solvents are used in the production process. This is recited in claim 1 by the language "free from toxicologically dangerous organic solvents." See page 6, line 37 to page 7, line 2 of the present specification which discloses that "toxicologically dangerous organic solvents include in particular chloroform, methylene chloride, fairly long-chained alcohols such as hexanol and octanol, but also ethanol in fairly high concentrations."

The product by Davis always contains organic solvent residues, even when they are only in the lower ppm concentration range.

The Examiner argues on page 11 of the Office Action that:

> Furthermore, Davis also teaches removing **at least most of** any co-solvent that is present. Additionally, one of ordinary skill in the art would be able to determine suitable solvents, which would not be deemed detrimental to the formation itself. Furthermore, the applicant's arguments that 'no organic solvents are used in the production process' is not persuasive since the instant pending claims are composition claims and it is the patentability of the composition itself that must be established. Davis teaches a **similar** composition for a **similar** intended purpose as the applicants. (emphasis added)

The Examiner basically admits that Davis does not anticipate the claimed invention, but rather only teaches a "similar" composition. A rejection under Section 102 requires more than disclosure of mere similarities: it requires disclosure of "every aspect of the claimed invention either explicitly or impliedly." See MPEP § 706.02(a). The Examiner has not shown how Davis teaches explicitly or impliedly to make a composition (1) containing no organic solvents or even residues of organic solvents, and (2) a supersaturation amount of drug.

Furthermore, Applicant did not merely argue process limitations. Instead, Applicant argued that the presently claimed invention does not contain any organic solvents, or organic solvent residues, because there are no organic solvents used to

prepare the composition. This argument goes right to the patentability of the claimed composition, "no organic solvent residues present."

The Examiner's argument that "one of ordinary skill in the art would be able to determine suitable solvents, which would not be deemed detrimental to the formation itself" is immaterial and demonstrates that the Examiner admits that organic solvents are present in the composition of Davis. The Examiner also admits that Davis teaches that the composition contains organic residues by arguing that "at least most of the co-solvent" in Davis removed. A composition that contains organic residues cannot anticipate the claimed invention, which excludes such organic residues.

Moreover, in a pharmaceutical formulation the excipients should have a tolerability as high as possible. Based on this approach, it is in any case better to use no organic solvent at all than using one – independent whether its toxicity is low or not. Nevertheless, the Examiner's reliance on weather the organic solvent is detrimental is immaterial to a patentability determination under Section 102.

> The Examiner argues in the Advisory Action dated April 27, 2004 that:
> The instant claims state 'free from toxicologically dangerous solvents and do not state 'free of solvents.' The argument that the solvents may contain toxicological problems are not supported by scientific evidence. Furthermore, it is not clear how the phrase 'toxicological dangerous solvents' provides a crisp distinction over other solvents that are used to form emulsions as desired by applicant.

Applicant first points out that the Examiner is misinterpreting the claims. Claim 1 clearly states "free from toxicologically dangerous **organic** solvents." Applicant does not exclude all solvents, such as water, which is an inorganic solvent. The language "free from toxicologically dangerous organic solvents" provides a clear distinction from other solvents used in the emulsion, such as water, which is an inorganic solvent. Furthermore, this language also provide a clear distinction in that it excludes even residues of organic solvents used in the process of Davis.

The use of "comprising" in claim 1 does not bring back into the claim what is specifically excluded by the claim language. For the Examiner to now argue that use

of "comprising" overrides or trumps all other claim language would overturn over 100 years of patent law.

The Examiner argues on pages 11 and 12 of the Office Action that:

> The applicants argument that the instant invention allows the incorporation of the drug beyond the concentration soluble in the oil and water phase of the emulsion was not found to be persuasive, since Davis explicitly teaches emulsions that are stable and reduce the toxicity of the drug.
>
> Applicant's arguments regarding the maximum concentrations of drug being soluble are also not persuasive, since generally, differences in concentration (or temperature) will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration (or temperature) is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). The prior art clearly recognizes the generic concept of formulation a stable oil-in-water emulsion comprising poorly soluble active ingredients.

Applicant respectfully submits that the present invention is not mere optimization as alleged by the Examiner. One of ordinary skill in the art cannot optimize what is not taught. If the prior art teaches that the maximum concentration of a drug is 1 ppm, one skilled in the art would not ignore this teaching and "optimize" the concentration of the drug to be greater than 1 ppm, i.e. outside the concentration limit of the drug. Essentially, the Examiner is arguing that one skilled in the art would ignore teachings in Davis to use the maximum concentration level, and now use a supersaturation concentration outside of those teachings. This is contrary to patent law. Those skilled in the art follow the teachings of the prior art, they do not do the opposite of what the prior art teaches as alleged by the Examiner.

In fact, Davis teaches in a direction away from the claimed invention. Davis teaches to use only the maximum concentration level. In contrast, the claimed invention teaches a composition containing supersaturation levels of drug.

The Examiner states there is no evidence that supersaturation levels are critical. This argument by the Examiner will be addressed in response to the Section 103 rejection below since it is immaterial in a Section 102 rejection.

According to Davis a concentration of 0.5 mg/l can be achieved when using 1.2% lecithin and 10% soya oil in the emulsion (90ml mixture of water, lecithin and drug plus 10 ml oil, Example 1). The loading can be increased to 1 mg/ml when increasing the lecithin to 1.8% and the oil to 20%. These concentrations represent the maximum amount of drug being soluble in the oil and water phase, i.e. the saturation solubility of the drug in these emulsions.

In contrast, the present invention allows the incorporation of the drug beyond the concentration soluble in the oil and water phase of the emulsion. Even when using only 1.2% lecithin, the present invention can incorporate 2mg/ml Amphotericin B. The present invention can use a concentration above the saturation solubility and double the amount which can be achieved by Davis even when using the higher lecithin concentration of 1.8%.

The Examiner argues in the April 27, 2004 Advisory Action that:

> Burden is placed on applicant to show that the drug dissolved in a solvent in the presence of a surfactant would not be sufficient to provide a super-saturated formulation in the aqueous phase. Note that the prior art teaches the dose to be determined by the skilled man and that the drugs in the prior art references are those that are poorly soluble. Additionally, the prior art is interested in long-term stability as shown in Examples 4 & 5.

Applicant submits that it is the Examiner's burden to provide a *prima facie* showing of how the prior art teaches the claimed invention. The Examiner cannot pass this burden onto Applicant. Simply put, the prior art does not teach or even suggest supersaturation and the Examiner has not shown otherwise. In rebuttal, the Examiner simply argues that is Applicant's burden to show how some theoretical composition containing a drug dissolved in a solvent in the presence of a surfactant does not "provide a supersaturated formulation in the aqueous phase." However, Applicant will

nontheless meet this newly minted burden. See page 5, lines 1-10 of the present specification, which teaches that:

> Surprisingly, it has now been found that the production of an emulsion system with dissolved active ingredient is also possible direct from the solid aggregate condition of the active ingredient. To produce the dispersion according to the invention, the active ingredient is added to the aqueous phase or the oil phase in particle form and then all components are subjected to a fairly high- or high-energy process such as, for example, homogenization, especially high pressure homogenization. The high-energy process of high pressure homogenization leads to incorporation of the active ingredient into the emulsion by molecular dispersion, and no active ingredient crystals remain detectable in the polarization microscope. The emulsions obtained surprisingly have a stability similar to that of systems produced using organic solvents. (emphasis added)

Since the cited references do not teach or suggest these process steps they cannot teach or suggest the formation of a stable supersaturated emulsion.

Based on the extensive arguments and citations to the prior art shown above, the prior art clearly teaches to form normal saturation of drugs, i.e. drugs dissolved at their solubility level. Drug solubility is well known and established in the prior art. The cited prior art attempts to solve the problem of low solubility in water by adding organic solvents. Even adding organic solvents will not provide a supersaturated formulation. Applicant solves the problem of low solubility by providing a stable supersaturated formulation, in the absence of such organic solvents. Applicant fails to see how a newly minted burden to demonstrate the absence of supersaturation of a drug alleviates the Examiner's burden to show how the prior art teaches or even suggests to form supersaturated formulations.

The fact that the cited prior art teaches the desirability of long-term stability is irrelevant. The cited prior art does not teach or even suggest forming supersaturated formulations free of organic solvents and, thus, they cannot teach how to form a long term stable supersaturated formulation that is free of organic solvents.

The present invention creates supersaturated emulsions, which are not disclosed in Davis. On the contrary, Davis teaches clear limits for the maximum drug incorporation. For this reason alone, Davis cannot anticipate the claimed invention.

Davis also does not disclose that the active drug can be present in solid crystalline form as recited in claim 2. Davis requires that the drug be dissolved. For this reason alone, claim 2 cannot be anticipated by Davis.

Davis also does not disclose the specific crystal sizes recited in claims 3-11. Davis requires that the drug be dissolved. For this reason alone, claims 3-11 cannot be anticipated by Davis.

In view of the admitted differences between Davis and the claimed invention, the claimed invention cannot be anticipated by Davis and withdrawal of the Section 102 rejection is respectfully requested.

II. **Claims 1-11, 19-25, 33-35, 37-45, 48, 55-57, 61-63, 143, 144, 146 and 148 are patentable under 35 U.S.C. § 102(b) over U.S. patent No. 5,616,330 (Kaufman).**

In the final Office Action, the Examiner rejected claims 1-11, 19-25, 33-35, 37-45, 48, 55-57, 61-63, 143, 144, 146 and 148 under 35 U.S.C. § 102(b) as being anticipated by U.S. patent No. 5,616,330 (Kaufman). The claimed invention is not anticipated by Kaufman for the following reasons.

The Examiner argues on page 10 of the final Office Action that:

> The applicant's arguments that organic solvents are not excluded in Kaufmann was not found to be persuasive since one of ordinary skill in the art would be able to determine acceptable or suitable solvents and one of ordinary skill in the art would be able to differentiate between ingredients that may or may not be detrimental to the formulation itself. Since Kaufmann utilizes pharmaceutically acceptable solvents in a stable

> oil-in-water emulsion and also teaches that his formulation provides for a stable emulsion having **minimal side effects**, it would be recognized that these solvents would not, in effect or nature, be toxicologically dangerous to the formulation. Furthermore, the examiner notes that the instant claims use "comprising" claim language, and hence permits the use of additional components asides from those recited in the claims. (emphasis added)

First, Applicant once again points out that the use of "comprising" in claim 1 does not bring back into the claim what is specifically excluded by the claim language. For the Examiner to now argue that use of "comprising" overrides or trumps all other claim language would overturn over 100 years of patent law.

The "minimal side effects" stated by the Examiner are completely avoided in the claimed composition because there are no organic solvents used in the production of claimed composition and, thus, there are no organic solvents or even residues of such organic solvents present in the composition. The Examiner basically admits that Kaufmann teaches a composition containing the organic solvents. For this reason alone, Kaufmann cannot anticipate the claimed invention, which does not contain such organic solvents.

The fact that "one of ordinary skill in the art would be able to differentiate between ingredients that may or may not be detrimental to the formulation itself" is immaterial to weather Kaufmann anticipates the claimed invention.

On pages 12 to 13 of the final Office Action, the Examiner argues that:

> Kaufmann discloses stable oil-in-water emulsions for intravenous administration incorporating a poorly soluble drug (taxol) in combination with suitable oils, emulsifiers, additives and water. It is deemed obvious to one of ordinary skill in the art to effectively distinguish between ingredients that may or may not be detrimental to the formulation itself. Since Kaufmann utilizes pharmaceutically acceptable solvents in a stable oil-in-water emulsion and also teaches that his formulation provides for a stable emulsion having minimal side effects, it would be recognized that these solvents would not, in effect or nature, be toxicologically dangerous to the formulation. Hence, the applicants arguments that solvents are incorporated in the invention of Kaufmann is not persuasive. The applicants arguments regarding the maximum concentrations of drug

> being soluble are also not persuasive, since generally, differences in concentration (or temperature) will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration (or temperature) is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." The prior art clearly recognizes formulations of stable oil-in-water emulsions, which comprise poorly soluble active ingredients and therefore, the incorporation of solvents would not adversely affect the composition.

The Examiner plainly admits that Kaufmann's composition contains organic solvents. In contrast, the claimed invention excludes these organic solvents. The Examiner's explanations as to why Kaufmann contains these organic solvents is immaterial to a Section 102 rejection. As stated previously, a rejection under Section 102 requires more than disclosure of mere similarities: it requires disclosure of "every aspect of the claimed invention either explicitly or impliedly." See MPEP § 706.02(a). The Examiner has not shown how Kaufmann teaches explicitly or impliedly to make a composition containing (1) no organic solvents or even residues of organic solvents, and (2) supersaturation of a drug. For this reason alone, the Examiner has not presented a prima facie case of anticipation and the Section 102 rejection should be withdrawn.

Applicant again respectfully submits that the present invention is not mere optimization as alleged by the Examiner. One of ordinary skill in the art cannot optimize what is not taught. If the prior art teaches that the maximum concentration of a drug is 1 ppm, one skilled in the art would not ignore this teaching and "optimize" the concentration of the drug to be greater than 1 ppm. Essentially, the Examiner is arguing that one skilled in the art would ignore teachings in Kaufmann to use the maximum concentration level, and now use a supersaturation concentration outside of those teachings. This is contrary to patent law. Those skilled in the art follow the teachings of the prior art, they do not do the opposite of the prior art.

In fact, Kaufmann teaches in a direction away from the claimed invention. Kaufmann teaches to use only the maximum concentration level. In contrast, the claimed invention teaches a composition containing supersaturation levels of drug.

The Examiner states there is no evidence that supersaturation levels are critical. This argument by the Examiner will be addressed in response to the Section 103 rejection below since it is immaterial in a Section 102 rejection.

Kaufmann also does not disclose that the active drug can be present in solid crystalline form as recited in claim 2. Kaufmann requires that the drug be dissolved. For this reason alone, claim 2 cannot be anticipated by Kaufmann.

Kaufmann also does not disclose the specific crystal sizes recited in claims 3-11. Kaufmann requires that the drug be dissolved. For this reason alone, claims 3-11 cannot be anticipated by Kaufmann.

In view of the many differences between Kaufmann and the claimed invention, Kaufmann cannot anticipate the claimed invention and withdrawal of the Section 102 rejection is respectfully requested.

III. Claims 1-15, 19-66, 143, 144, 146 and 148-150 are patentable under 35 U.S.C. § 103 over Davis alone or Kaufman alone.

In the final Office Action, the Examiner rejected claims 1-15, 19-66, 143, 144, 146 and 148 under 35 U.S.C. ' 103 as being unpatentable over Davis alone or Kaufman alone. The claimed invention is not taught or suggested by either of Davis or Kaufman for the following reasons.

The Examiner argues in regards to the Section 102 rejections above that there is no evidence that supersaturation levels are critical. Applicant once again points out the criticality of the claimed invention, which is not taught or suggested by the cited prior art.

According to the present invention, it is surprisingly possible to enter the supersaturated concentration range without precipitation of drug crystals during

storage. This is achieved by the novel production technology discovered and disclosed in the present application, for example, co-homogenization of drug powder and oil in water. In contrast, it is well known throughout the art, that supersaturation of drugs in a carrier provides an unstable composition in which the drug crystallizes out of solution over time. The cited references are in agreement with this by only teaching to use compositions containing drugs at there solubility limit.

Furthermore, at supersaturation levels, the claimed invention is able to provide a dose containing far less carrier than the prior art compositions. Thus, any undesirable effects due to the carrier are substantially reduced in the present invention.

Moreover, the claimed composition does not contain any organic solvents. In contrast the cited prior art contains organic solvents. Even the "minimal side effects" caused by the organic solvents alluded to by the Examiner are completely avoided by the present invention.

Davis:

On page 14 of the final Office Action, the Examiner argues that:

> Davis teaches an oil-in-water emulsion which provides long-term stability. It is the patentability of the composition, per se that must be established. Davis recognizes the concept of intravenous delivery of poorly soluble drugs and teaches the effective delivery of non-toxic amounts of emulsion. One of ordinary skill in the art would be able to determine suitable saturation concentrations through the use of routine or manipulative experimentation, based on the intended purpose, since these are viewed as variable parameters.

Davis teaches clear limits to the drug concentrations, i.e. the solubility of the drug. For example, Davis discloses up to 1 mg/ml, preferably 0.5mg/ml of Amphotericin (column 4, lines 14-16). Davis only teaches to dissolve the drug in amounts up to the saturation concentration of the drug in the oil and water.

In contrast, the claimed composition provides supersaturated concentrations of drug, such that the drug crystals do not precipitate out of solution over time. The

Examiner does not provide any evidence or convincing argument that one of ordinary skill in the art would now ignore the teachings of Davis and go above the saturation limits of the drug and provide a stable supersaturated drug.

Once again, Applicant submits that it is not routine experimentation to ignore teachings of the prior art and use concentrations outside of the disclosed ranges as alleged by the Examiner, especially not supersaturation concentrations that are well-known to be unstable. For this reason alone, the Section 103 rejection should be withdrawn.

The Examiner essentially argues on pages 4-6 of the Office Action that known emulsions using similar compositions of excipients can be administered by the same routes and have similar sizes. However, this does not apply to drugs for the reasons discussed below.

The Examiner denies any significant distinction between Davis and the present invention. A main difference overlooked by the Examiner is the achieved drug loading: (1) the saturation concentration with Davis and Kaufmann; and (2) in the supersaturation range in the present invention.

According to the Examiner, Davis teaches similar amounts of drug incorporated in the suspension compared to the present invention (page 6, third paragraph of Office Action). Davis discloses up to 1 mg/ml, preferably 0.5mg/ml of Amphotericin (column 4, lines 14-16). Davis only teaches to dissolve the drug in amounts up to the saturation concentration of the drug in the oil and water. In the present invention, going beyond this saturation limit and even doubling the saturation solubility is unexpected and something which was not predictable from Davis. Davis does not teach supersaturation of drugs. The instant invention can, for example, produce emulsions with 5mg/ml Amphotericin (supersaturated), Davis cannot.

Applicant believes the invention works in the following manner but is not bound by this theory. Applicant's belief about the mechanism have been submitted for publication to the Int. J. Pharm. The drug is believed to be not molecularly dispersed in the lecithin layer, and it seems to form "molecular nano-arrangements," which allow a

much higher drug incorporation than molecular dissolution in the lecithin. These special arrangements in the interfacial layer are generated by the novel production method disclosed in the present application. It is speculated that the high energy input in the presence of a high drug concentration leads to the formation of such nanostructures and increased loading capacity. Previously, homogenization with such high drug concentration was not tried because it appeared to be nonsense. It was expected that drug concentrations above the saturation solubility in the emulsion could not be incorporated and would remain as sediment. Just the opposite was surprisingly found in the instant invention.

Applicant respectfully submits that the Examiner is not correct in stating that the prior art teaches suitable concentration to arrive at stable emulsions. The prior art concentrations are not sufficiently high to obtain acceptable injection volumes. The previous emulsions are at the or even below the saturation concentration, i.e. they are not supersaturated emulsions. The emulsions of the invention are also stable, but the key feature is the supersaturation, which provides suitable injection volumes. Applicant submits that it is unfair for the Examiner to compare the stability of a drug composition disclosed in Davis, in which the drug is present at a concentration at or below the solubility limit, with the present invention, in which the drug is present at a concentration above the solubility limit. Of course, the drug will remain in solution if it is at or below it solubility limit. That is the definition of solubility. However, it is now quite unexpected that a drug can be stabilized above its solubility limit in the claimed composition.

Kaufmann:

On pages 14 to 15 of the Office Action, the Examiner argues that:

> The teachings of Kaufmann have been discussed above. Kaufmann teaches stable oil-in-water emulsions for poorly soluble active ingredients. The applicants arguments that there is no teaching in either reference to exclude the use of organic solvents is not persuasive since the instant claims use "comprising" claim language, and thus the incorporation of additional ingredients, asides from those recited are not excluded from the

> claims. The prior art teaches stable emulsions incorporating solvents, however, since these solvents are routinely used in the pharmaceutical art, they would not be considered detrimental or toxic to the formulation. Hence, the instant invention is rendered obvious and unpatentable over the prior art.

Applicant once again points out that the use of "comprising" in claim 1 does not bring back into the claim what is specifically excluded by the claim language. For the Examiner to now argue that use of "comprising" overrides or trumps all other claim language would overturn over 100 years of patent law.

The Examiner's argument that "since these solvents are routinely used in the pharmaceutical art, they would not be considered detrimental or toxic to the formulation" is immaterial. Any side effects due to organic solvents is detrimental to the patient. In the present invention, all side effects due to organic solvents are avoided since no organic solvents are present. The prior art does not teach or suggest avoiding all side effects by using a composition containing no organic solvents.

The Examiner points out the different excipients used by Kaufmann and also the different taxines. Kaufmann teaches the amount of 0.1% to 1% taxine in the emulsions which, according to the Examiner, are in the range of the present invention. However, one cannot compare incorporation of one drug (Amphotericin) directly with another drug (in this case taxine). It might be easy to incorporate drug A (e.g. taxine) in a concentration of 1% in case the saturation solubility in the emulsion is well above, e.g. 5%. However, even when incorporating 1% of drug B, this represents a major achievement when the saturation solubility of B is only e.g. 0.1%. From this, direct comparison on the basis of just percentages is not possible. The solubility of each drug must also be considered.

Furthermore, according to the present invention, concentrations of 5 and 10mg/ml can be incorporated, the latter by using an emulsion with crystalline fraction. In addition, Kaufmann clearly teaches using Cholesterol to solubilize the drug. This means that Kaufmann is working with an oil phase <u>at the maximum solubility</u>. The

instant invention is working well above the saturation solubilities. In contrast to Kaufmann, the present invention is a supersaturated system.

As discussed above, the supersaturated system according to the present invention is unexpected and provides many advantages over the conventional maximum solubility system of Kaufmann.

Applicant submits that it is improper for the Examiner to compare the stability of a drug composition disclosed in Kaufmann, in which the drug is present at a concentration at or below the solubility limit, with the present invention, in which the drug is present at a concentration above the solubility limit. Of course, the drug will remain in solution if it is at or below it solubility limit. That is the definition of solubility. However, it is now quite unexpected that a drug can be stabilized above its solubility limit in the claimed composition.

Furthermore, both Davis and Kaufmann teach using organic solvents, which are excluded by the present invention. There is no teaching in either reference to exclude the use of organic solvents.

Davis and Kaufmann do not disclose that the active drug can be present in solid crystalline form as recited in claim 2. Davis and Kaufmann both require that the drug be dissolved, which is in a direction opposite to that of solid drug crystals. For this reason alone, claim 2 cannot be obvious over Davis or Kaufmann.

Davis and Kaufmann also do not disclose the specific crystal sizes recited in claims 3-11. Davis and Kaufmann both require that the drug be dissolved. For this reason alone, claims 3-11 cannot be obvious over Davis or Kaufmann.

Claims 64-66 recite that the active ingredient dissolved is greater than the additive quantity by a factor of 2, factor of 5, or a factor of 10. Since neither of Davis or Kaufmann teach how to make a dispersion containing the active ingredient dissolved in quantities greater than a factor of 1 (normal solubility), neither of the cited references can make obvious supersaturation at a factor of 2, 5 and especially 10 times the normal solubility. For these reasons, claims 64-66 are not obvious over Davis or Kaufmann.

Claims 149 and 150 are not obvious over Davis and Kaufmann for the many reasons provided above. Furthermore, claims 149 and 150 recite the language "organic solvent-free." The Examiner has not provided a prima facie case of obviousness showing how the prior art formulations are "organic solvent-free." On the contrary, the Examiner admits that the cited prior art teaches to use organic solvents. Thus, the prior art teaches away from the invention of claims 149 and 150.

In view of the many differences between the present invention and Davis or Kaufmann, and the many unexpected advantages of the present invention, withdrawal of the Section 103 rejection is respectfully requested.

Conclusion

In view of the lack of *prima facie* case of anticipation and/or obviousness, the many differences between the claimed invention and the cited references, and the unexpected advantages of the claimed invention, it is believed that this application clearly and patentably distinguishes over the combination of the cited references and is in proper condition for allowance. Accordingly, Appellants respectfully request that the Board allow claims 1-15, 19-66, 143, 144, 146 and 148-150 over the cited references.

Respectfully submitted,

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APPENDIX

1. Dispersion which comprises:

an oily phase;

an aqueous phase, in the form of an oil-in-water emulsion or a water-in-oil emulsion; and

at least one active ingredient that is only slightly or with difficulty soluble in the oily phase and the aqueous phase, wherein the dispersion is free from toxicologically dangerous organic solvents and contains the active ingredient dissolved in a quantity that is greater than the quantity which results additively from its maximum solubility in the oily and the aqueous phase of the emulsion.

2. Dispersion according to claim 1, wherein the active ingredient, in addition to the dissolved state, is partially present in highly dispersed solid crystalline form, resulting in a dispersion with a heterogeneously dispersed phase of oil drops and active ingredient crystals.

3. Dispersion according to claim 2, wherein at least 90% of the active ingredient crystals present are smaller than 5 µm, volume distribution determined by laser diffractometry.

4. Dispersion according to claim 2, wherein at least 95% of the active ingredient crystals present are smaller than 5 µm, volume distribution determined by laser diffractometry.

5. Dispersion according to claim 2, wherein about 100% of the active ingredient crystals present are smaller than 5 µm, volume distribution determined by laser diffractometry.

6. Dispersion according to claim 2, wherein at least 90% of the active ingredient crystals present are smaller than 3 μm, volume distribution determined by laser diffractometry.

7. Dispersion according to claim 2, wherein at least 95% of the active ingredient crystals present are smaller than 3 μm, volume distribution determined by laser diffractometry.

8. Dispersion according to claim 2, wherein about 100% of the active ingredient crystals present are smaller than 3 μm, volume distribution determined by laser diffractometry.

9. Dispersion according to claim 2, wherein at least 90% of the active ingredient crystals present are smaller than 1 μm, volume distribution determined by laser diffractometry.

10. Dispersion according to claim 2, wherein at least 95% of the active ingredient crystals present are smaller than 1 μm, volume distribution determined by laser diffractometry.

11. Dispersion according to claim 2, wherein about 99% of the active ingredient crystals present are smaller than 1 μm, volume distribution determined by laser diffractometry.

12. Dispersion according to claim 1, wherein the dispersion comprises an oil-in-water emulsion and contains about 5 to about 99.5 wt.% of aqueous phase, based on the total weight of the dispersion.

13. Dispersion according to claim 1, wherein the dispersion comprises an oil-in-water emulsion and contains about 10 to about 95 wt.% of aqueous phase, based on the total weight of the dispersion.

14. Dispersion according to claim 1, wherein the dispersion comprises an oil-in-water emulsion and contains about 60 to about 95 wt.% of aqueous phase, based on the total weight of the dispersion.

15. Dispersion according to claim 1, wherein the dispersion comprises an oil-in-water emulsion and contains about 70 to about 95 wt.% of aqueous phase, based on the total weight of the dispersion.

19. Dispersion according to claim1, wherein the dispersion contains at least one selected from the group consisting of emulsifiers and stabilizers.

20. Dispersion according to claim 19, wherein the dispersion contains less than 15 wt.% of emulsifiers and/or stabilizers, based on the total weight of the dispersion.

21. Dispersion according to claim 19, wherein the dispersion contains less than 10 wt.% of emulsifiers and/or stabilizers, based on the total weight of the dispersion.

22. Dispersion according to claim 19, wherein the dispersion contains less than 2 wt.% of emulsifiers and/or stabilizers, based on the total weight of the dispersion.

23. Dispersion according to claim 19, wherein the dispersion contains from about 0.6 to about 1.2 wt.% of emulsifiers and/or stabilizers, based on the total weight of the dispersion.

24. Dispersion according to claim 1, wherein the dispersion comprises at least one emulsifier selected from the group consisting of egg lecithin, soya lecithin, phospholipids of egg or soya, sorbitan esters, sorbitane trioleate, polyethylene glycol sorbitan esters, polyoxyethylene sorbitane monooleate, sodium glycocholate, sodium lauryl sulphate, and mixtures thereof.

25. Dispersion according to claim 1, wherein the dispersion comprises at least one stabilizer selected from the group consisting of block co-polymers, poloxamers, Poloxamer 188 and 407, poloxamines, Poloxamine 908, polyvinyl pyrrolidone, polyvinyl alcohol, gelatine, polysaccharide, hyaluronic acid, chitosan, derivatives of chitosan, polyacryl acid, derivatives of polyacryl acid, polycarbophil, cellulose derivatives, methyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sugar esters, saccharose monostearate, sodium citrate individually, and mixtures thereof.

26. Dispersion according to claim 1, wherein the dispersion comprises an oil-in-water emulsion and the oil phase used for the preparation of the dispersion comprises lipids which are solid at room temperature.

27. Dispersion according to claim 1, wherein the dispersion comprises an oil-in-water emulsion and the oil phase used for the preparation of the dispersion comprises lipids which are liquid at room temperature.

28. Dispersion according to claim 1, wherein the dispersion comprises an oil-in-water emulsion and the oil phase used for the preparation of the dispersion comprises a mixture of one or more lipids which are liquid at room temperature with one or more lipids which are solid at room temperature.

29. Dispersion according to claim 28, wherein the mixture of liquid lipid : solid lipid varies from about 99:1 to about 1:99 parts by weight.

30. Dispersion according to claim 29, wherein proportion of liquid lipid in mixture of lipids is at least 10 parts by weight.

31. Dispersion according to claim 29, wherein proportion of liquid lipid in mixture of lipids is at least 30 parts by weight.

32. Dispersion according to claim 29, wherein proportion of liquid lipid in mixture of lipids is at least 50 parts by weight.

33. Dispersion according to claim 1, wherein the oil phase comprises at least one individual lipid or mixtures thereof selected from the group consisting of natural and synthetic triglycerides, natural and synthetic monoglycerides, natural and synthetic diglycerides, self-emulsifying modified lipids, natural and synthetic waxes, fatty alcohols, esters of fatty alcohols, ethers of fatty alcohols, hard wax, Imwitor 900, glycerol trilaurate, glycerol myristate, glycerol palmitate glycerol stearate, glycerol behenat, waxes, cetyl palmitate, carnauba wax, white wax, hydrocarbons, and hard paraffin.

34. Dispersion according to claim 1, wherein the an oil phase comprises at least one selected from the group consisting of soya oil, safflower oil, long-chain triglycerides, medium-chain triglycerides, miglyols, fish oils, oils with an increased constituent of unsaturated fatty acids, and acetylated partial glycerides.

35. Dispersion according to claim 1, wherein the aqueous phase comprises water or mixtures of water with water-miscible organic liquids.

36. Dispersion according to claim 1, wherein the aqueous phase comprises water and at least one liquid polyethylene glycol.

37. Dispersion according to claim 1, wherein the aqueous phase contains at least one additive selected from the group consisting of electrolytes, non-electrolytes, glycerol, glucose, mannitol, xylite, gel forming agents, cellulose, and cellulose derivatives.

38. Dispersion according to claim 1, wherein the liquid and oily phase comprises at least one oil-in-water emulsion selected from the group consisting of Lipofundin, Intralipid, Lipovenoes, Abbolipid, Deltalipid and Salvilipid.

39. Dispersion according to claim 1, wherein the active ingredient is selected from the group consisting of medical drugs for treatment of human or animal bodies.

40. Dispersion according to claim 1, wherein the dispersion contains one or more active ingredients selected from the group consisting of anaesthetics, antibiotics, antimycotics, antiinfectives, corticoids, hormones, antiestrogens antiseptics, vasoactivating agents, glauco agents, beta blocker, cholinergics, sympathomimetics, carboanhydrase inhibitors, mydriatics, virustatics, agents for tumor therapy, antiallergics, vitamins, antiinflammytory drugs, immuno-supressives, ciclosporine, and any combination thereof.

41. Dispersion according to claim 1, wherein the dispersion is positively charged.

42. Dispersion according to claim 1, wherein the dispersion comprises at least one positively charged stabilizer.

43. Dispersion according to claim 1, wherein the dispersion comprises at least on positively charged stabilizer selected from the group consisting of sodium lauryl sulfate, stearylamine, positively charged phospholipids, and positively charged lipids.

44. Dispersion according to claim 1, wherein the dispersion comprises an oil-in-water emulsion adapted for intravenous injection, and wherein the dispersion comprises at least on positively charged stabilizer.

45. Dispersion according to claim 44, wherein the dispersion further includes at least one lecithines or nonionic stabilizers.

46. Dispersion according to claim 44, wherein the dispersion further comprises at least one poloxamer polymer.

47. Dispersion according to claim 1, wherein the active ingredient comprises ciclosporine.

48. Dispersion according to claim 1, wherein the active ingredient comprises at least one selected from the group consisting of anti-mycotics, Amphotericin B, anti-infectives, Buparvaquone, Atovaquone, immuno-suppressives, Cyclosporin A, natural and synthetic derivatives of Cyclosporin A, tumor therapy drugs, Paclitaxel, and Taxotere.

49. Dispersion according to claim 1, wherein the active ingredient has a solubility of less than 1 part per 100 parts in the aqueous phase.

50. Dispersion according to claim 1, wherein the active ingredient has a solubility of less than 1 part per 1000 parts in the aqueous phase.

51. Dispersion according to claim 1, wherein the active ingredient has a solubility of less than 1 part per 10,000 parts in the aqueous phase.

52. Dispersion according to claim 1, wherein the active ingredient has a solubility of less than 1 part per 100 parts in the oily phase.

53. Dispersion according to claim 1, wherein the active ingredient has a solubility of less than 1 part per 1000 parts in the oily phase.

54. Dispersion according to claim 1, wherein the active ingredient has a solubility of less than 1 part per 10,000 parts in the oily phase.

55. Dispersion according to claim 1, wherein the size of water phase and oily phase droplets is less than about 10 μm.

56. Dispersion according to claim 1, wherein the size of water phase and oily phase droplets is less than about 5 μm.

57. Dispersion according to claim 1, wherein the size of water phase and oily phase droplets is less than about 1 μm.

58. Dispersion according to claim 1, wherein a pH of the dispersion is between 4 and 8.

59. Dispersion according to claim 1, wherein a pH of the dispersion is between 5 and 7.5.

60. Dispersion according to claim 1, wherein a pH of the dispersion is between 6 and 7.5.

61. Dispersion according to claim 1, wherein the active ingredient is present in an amount of from about 0.01 to about 30 wt.%, based on the total weight of the dispersion.

62. Dispersion according to claim 1, wherein the active ingredient is present in an amount of from about 0.1 to about 10 wt.%, based on the total weight of the dispersion.

63. Dispersion according to claim 1, wherein the active ingredient is present in an amount of from about 1 to about 5 wt.%, based on the total weight of the dispersion.

64. Dispersion according to claim 1, wherein the quantity of active ingredient dissolved is greater than the additive quantity by a factor of 2.

65. Dispersion according to claim 1, wherein the quantity of active ingredient dissolved is greater than the additive quantity by a factor of 5.

66. Dispersion according to claim 1, wherein the quantity of active ingredient dissolved is greater than the additive quantity by a factor of 10.

143. A medicament comprising the dispersion according to claim 1.

144. A medicament for treatment of mycoses, inflammations, allergic diseases, tumor diseases, cardiovascular diseases, viral and other infections, or for conducting anaesthetic treatment comprising a dispersion according to claim 1.

146. A medicament which can be administered intravenously, intra- and subcutaneously, intramuscularly, intra-articularly or intraperitoneally comprising a dispersion according to claim 1.

148. A medicament which has a prolonged residence time in the blood, compared to negatively charged dispersions, comprising a dispersion according to claim 1.

149. Dispersions in form of an oil-in-water emulsion comprising:

an oil phase;

a water phase;

one or more surfactants or stabilizers; and

one or more drugs being only slightly or poorly soluble in the water and in the oil, the dispersions are supersaturated and contain an incorporated amount of the drug in dispersion that is higher than the additive solubility calculated from the drug solubility in the oil and water phases of the dispersion, and the dispersions are organic solvent-free.

150. Dispersions according to claim 149, wherein the concentration of surfactant, stabilizer or mixtures of surfactants and stabilizers is between 0.1% and 20% by weight.